Reviews.

1.—Researches on the Nature and Treatment of Diabetes. *By* F. W. Pavy, M.D., F.R.S. Second Edition. Revised and Enlarged. London: J. Churchill & Sons. 1859.

In 1848, Dr Claude Bernard of Paris published the details of an interesting series of physiological experiments demonstrating the *constant presence of sugar in the animal economy in a state of health.* Until this period, it was believed that the vegetable kingdom alone possessed the power of forming sugar, and that any which might be found in the urine, blood, &c., must have been derived from saccharine or amylaceous food. Observing that plants obtained from the soil and from the atmosphere alone, the principles of the saccharine matter they so abundantly contain, M. Bernard set himself to determine the following questions:—Do animals form sugar in a similar manner by elaborating within their organs the primitive elements which compose sugar? or, is the sugar which is found in the animal body the product of the digestion of saccharine and amylaceous substances? The conclusions he deduced from his investigation were,—1. Sugar is constantly present in the blood of the heart and in the liver of man and of animals, and is found in the liver during the healthy process of assimilation. 2. Sugar is found in the animal economy independently of saccharine or amylaceous food. 3. Sugar is generated in the liver before the birth of the animal, and, consequently, before any direct ingestion of aliment of any kind. 4. The production of sugar is a function of the liver, and is connected with the integrity of the pneumogastric nerve. These views met with so much and so prompt confirmation by many experimental observers, that M. Bernard's *theories* and speculative *inferences* were received and adopted with his facts, and at once placed in all medical text-books. His highly original and memorable observations—or discoveries as they were termed—opened the way to farther researches, of which he continued the earnest pioneer. The principle itself, from which the sugar takes its origin in the liver, was soon after discovered and isolated; and, as sugar was supposed by Bernard to constitute its physiological purpose, this principle was named by him *glycogen*, or glycogenic matter.

While the brilliant character of Bernard's experiments, and the positive facts which he established were frankly acknowledged, his explanation and theoretical views underwent the searching scrutiny that in medicine is always accorded to novel doctrines, and several eminent men soon began to question the validity of the *theory of glycogenesis.*

That "in man and in all animals there is a sugar-producing organ, and this organ is the liver,"—that sugar is present in the liver, and "in no other organ of the body,"—that the sugar is "*secreted by the hepatic cells*,"—that "in the lung, the sugar being brought into contact with the air, and mixing with the whole mass of the blood, sometimes completely disappears,"—that "the blood which arrives at the lung contains sugar, while that which leaves it contains no trace of this constituent,"—that in respect to diet, "it is the nitrogenous element which serves to form the sugar,"—that "in a physiological state the ingestion of amylaceous or saccharine matter does not augment the quantity of sugar in the liver, and, consequently, in the animal economy generally," were some of the principal results which M. Bernard believed he had established. They were tacitly acquiesced in by the many, but were keenly scrutinised by a select few, among whom the foremost place must be accorded to our author, who has done very much to illustrate the whole subject, and whose name will assuredly be bound up in its history.

We have deemed it necessary to refer to some of the more prominent points of the subject, as it stood when Dr Pavy entered upon its examination, because the work now under consideration is a record of his painstaking enquiry. While we shall now endeavour to make our readers acquainted with so much of its important and interesting contents as will enable them to appreciate its great value, we beg at the same time to recommend the book itself for perusal and careful study.

In questioning the soundness of Bernard's glycogenic theory, Dr Pavy at the outset objects to the term made use of by Bernard in designating the sugar-forming material, in so far as it is used to imply a physiological destination. "It is true," he says, "that *after death*, and under certain *unnatural conditions*, it is a glycogenic or sugar-forming substance; but sufficient evidence will, I think, be advanced to show that, *under natural circumstances*, such is not the case." Dr Pavy prefers the term, "amyloid substance," a name simply implying that it is a body presenting an alliance to starch, and by this name it is now very generally called. He says:—

"I may state at the outset that I have nothing to say against the accuracy of the facts, taking them simply as facts, that have been put for-

ward by Bernard. Repeating Bernard's experiments, as he performed them, results are to be obtained, as I can personally testify, in strict accordance with the descriptions he has given. The question, however, raised by my researches is, whether unwarranted conclusions have not been drawn from them through a source of fallacy having been overlooked. For example, in Bernard's experiment the life of an animal that had been previously kept upon food devoid of starch and sugar was destroyed, and blood collected in an ordinary manner from certain parts of the circulatory system. It was found upon examination that the blood escaping from the liver was pretty abundantly charged with sugar, whilst that flowing to the organ was free, or, speaking more precisely, next to free from it. The liver also, unlike the other organs and tissues of the body, was found to contain a large quantity of sugar. Now, it is to be observed that these results, looked at strictly, only furnish evidence of the condition actually existing AFTER DEATH; but they have been taken as representing the *ante mortem* or physiological state. . . . It remains to be seen whether a different mode of experimenting does not show that the theory of glycogenesis has been raised upon a fallacious foundation. . . . The *ante mortem* and *post mortem* states, in other words, do not correspond."

Dr Pavy has, therefore, made a discovery which consists essentially in his demonstration of the fact, that instantly after death the chemical relation of the animal fluids and tissues are—at least in respect of the liver—completely altered, and present as marked and inexplicable phenomena as are witnessed in the changed condition of the blood which we recognise by the term "coagulation." A very few minutes suffices to effect this change; but Dr Pavy shows, by various ingenious methods, the possibility of "coming down, as it were,"—a favourite phrase of our author—upon the blood in its *living* or physiological state; and of arresting, for a sufficient time for observation, those changes which take place in the tissues, so that the precise condition in which they exist at the *instant* of death may be observed. There is, therefore, no time permitted by Dr Pavy's mode of experimenting for the occurrence of those *post mortem changes* which form the fallacious basis of Bernard's deductions. As a result of numerous and varied experiments, Dr Pavy finds that blood taken from the right side of the heart *a short time* after death is strongly saccharine; while if the heart is, with the least possible delay,—i.e., *instantly—excised* and removed after the *instantaneous* death of the animal, the blood in the right cavities of the heart is found as free from sugar as if it had been quietly drawn off by a catheter during life.

It is thus demonstrated that blood taken from the right side of the heart is not appreciably more saccharine than that derived from the arteries and veins. The same holds good with regard to the right ventricular blood, as compared with that of the portal vein; and yet, one of the principal arguments for the glycogenic theory is that the blood flowing *to the liver* is free

from sugar, while that flowing from the liver is said to be highly charged with sugar. "It seems, however," says Dr Pavy, "that no such difference, taking the blood in the condition belonging to life in reality, can be traced. . . . As a normal condition there is only a trace of sugar to be encountered in the blood between the liver and the lungs,—the same in fact that is also to be met on the other side of the lungs; in the blood returning from the system at large, and even in the blood that is flowing towards the liver. The blood, therefore, (viz., that escaping from the liver) which was formerly looked upon as affording the evidence upon which the glycogenic theory was founded, has nothing special belonging to it."

Having reached this carefully argued conclusion, and shown that Bernard's observations were so far imperfect and based on a fallacy, Dr Pavy leaves the subject of the state of *the blood*, and turns his attention to that of *the liver*, which has been reported to enjoy the glycogenic or sugar-forming function. He instituted observations directed "towards coming down upon the state of the organ in relation to sugar, as it were nearer to that of life, than had hitherto been done." The experiments by which he attained his object were repeated, and varied, and checked and counterchecked by so many ingenious devices, that his conclusions may, to our thinking, be accepted, as having been demonstrated in a manner as nearly perfect as any physiological fact can be. The animals experimented upon, chiefly the rabbit, were destroyed by pithing, freezing, oiling the skin, and by various other modes, and the liver was easily "*alighted upon* in a non-saccharine state, and found to become strongly saccharine afterwards." The liver itself was removed instantly after death, and subjected to the action of acids—of alkalis and of other chemical agents, and from the information supplied by these experiments our author "had no longer to look for conditions that prevented sugar from passing from the liver into the blood-vessels during life. *Sugar did not pass because it did not exist*, not being produced in the liver *during life* as it is after death."

"Such are the facts that became gradually and unexpectedly disclosed by the prosecution of experimental research, commenced with quite a different end in view from that which was arrived at. Originally a strong believer in, and the supporter of, the glycogenic doctrine, I was compulsorily led, by the unlooked for evidence that presented itself, to stand forward as an opponent to it. Taking a review of the results that have as yet been brought forward, the position of the matter may be said to stand thus:—The evidence upon which the liver was supposed to enjoy a sugar-forming function *was based upon conditions met with after death.* Now it happens to turn out that these conditions can be shown to *differ from those*

existing during life; and hence we are no longer justified in using them for the purpose they have hitherto been applied to, viz., as a foundation for conclusions regarding the physiological state. It is not that there is anything incorrect about Bernard's experimental results, as far as the results themselves are concerned; but what I have to speak against is, that inferences have been drawn from them which they do not, strictly speaking, warrant. The results I have been describing, as having been obtained by myself, are perfectly compatible, not with our former *conclusions*, it is true, but with the experiments from which these conclusions were drawn. From an ordinary examination of the liver, and of the blood of the right side of the heart after death, we obtain reactions indicative of the presence of a large quantity of sugar, and the deduction hitherto drawn has been that the sugar existed there as a natural condition of life. Such a deduction, however, is obviously gratuitous, all that can be strictly or logically inferred from such an examination is, that the liver and right ventricular blood are in a saccharine condition *after death.* To obtain evidence of the state that exists *during life* requires a different mode of experimenting, and from such it appears that error has arisen through overstepping the strict letter of interpretation that the original experiments will bear."

It was natural to anticipate that Dr Pavy's conclusions should be severely questioned, upsetting as they did the existing and seemingly well-established theory of Bernard, and modifying all the inferences that emanated from the discovery of that distinguished physiologist. In this country, Dr Harley,* as the result of special physiological experiments, in which he was assisted by Dr Sharpey, placed himself in opposition to Dr Pavy, and Dr Thudicum † soon after took independent grounds of exception in connection with certain of the chemical details. The objections of Dr Thudicum were easily set aside, while those of Dr Harley, who failed to obtain some of Dr Pavy's results, and maintained that as sugar is found in the liver at the moment of death it is no post mortem change but a natural condition, were likewise thoroughly silenced by the mass of confirmatory evidence of the soundness of Dr Pavy's views, supplied by independent observers in this country and on the Continent. In this country Dr R. M'Donnell,‡ who has become dexterous from frequent performance of the operation, in obtaining blood from the heart of a living animal by means of a catheter introduced into the right ventricle; and on the Continent Drs Schiff and Herzen,§ who adopt the plan of operating on the liver *instantly* after the death of the animal, while MM. Meissner and Jaeger ‖ excise portions of the liver of living animals. All these observers have obtained results which establish absolutely the

* Proc. Roy. Soc., No. 38, p. 289.
† *Brit. Med. Journal*, March, 1860.
‡ Dub. Hosp. Gaz., May, 1860; and in a special treatise on the Functions of the Liver. Dublin, 1865.
§ Journal de l' Anatom. et de la Physiologie. Paris, 1866.
‖ *Ibid.*

soundness of Dr Pavy's original researches and conclusions. It is, therefore, abundantly evident that the "amyloid substance" which is found existing in the liver in specially large quantity, is not transformed into sugar under *physiological* circumstances.

In his examination of the physiological aspect of the subject, our author makes numerous observations, which are highly important in a pathological and therapeutical point of view, and from their suggestive tendency, they should furnish useful practical deductions.

Dr Pavy had observed, in the course of his experiments, that the size of the liver was in a very marked manner influenced by the nature of the food, and that the difference observable was chiefly, if not entirely, dependent on a difference in the amount of amyloid substance present. With the special view of obtaining precise information on this point, he instituted and carried out several sets of experiments.

For several days prior to death, 11 dogs were fed on a strictly animal diet; 5 dogs were fed on meal and potatoes; and 4 dogs received, besides animal food, a daily allowance of 4 or 5 oz. of ordinary brown sugar. The animals were weighed just before death, the liver *immediately* after death. A piece of the liver was then examined, allowing as little time as possible to elapse for the loss of amyloid substance, *from post mortem* transformation into sugar.

Under an animal diet the liver weighed, as nearly as possible, *half-an-ounce for every pound* of the animal—the relative weight being 1 to 30. The amount of amyloid substance in the liver was 7.19 per cent.

Under vegetable food exclusively, the liver was found to be relatively of double size, weighing *one ounce for every pound*, the proportion being 1 to 15, while the amyloid substance was more than doubled, and amounted to 17.23 per cent.

Under a diet of animal food, with an admixture of sugar, the exact relative weight of the liver was 1 to 16½, a proportion closely corresponding with what was found under a vegetable diet, while the amyloid substance was as nearly as possible doubled.

From these, and from numerous other experiments, carried out by various methods, upon rabbits, &c., Dr Pavy ascertained that sugar introduced into the alimentary canal from without, is transformed into amyloid substance in the liver; and as these results have been confirmed by Dr M'Donnell and others, they show conclusively that amyloid substance is derivable from starch, sugar, &c., and so far they also are opposed to the glycogenic theory.

A very curious result was observed during these experiments. The liver, besides the extraordinary increase in volume which followed upon the use of sugar when added to animal food, underwent a change in its physical condition, which was equally remarkable. Under an animal diet, the organ is firm and tough, and requires the employment of a considerable force before it can be torn asunder by the fingers, in this respect resembling the ordinary condition of the organ in diabetic patients; but after the use of starch, sugar, &c., it becomes so soft as to be easily crushed, and to give way under the slightest pressure. This fact seems to us of considerable importance in a medico-legal point of view, and it ought to be kept in mind in homicidal cases, where the amount of violence used during life bears upon the question of a deadly intention to injure. The previous dieting of the individual may, in such cases, become a matter that will weigh heavily in the decision. Our memory has recorded an observation, for which we are at the moment unable to cite the authority, viz., that the grain-eating inhabitants of Hindostan (we think that was the locality specified) are peculiarly subject to rupture of the liver, as a result of blows and of falls. The circumstance also throws much light on the ability to sustain without injury the violent shocks that pugilists and acrobats, &c., undergo in the pursuit of their ordinary avocations.

Our space will not admit of extending farther our references to the numerous grounds on which Bernard's glycogenic theory is open to objections—such as the fact now freely admitted, and, indeed, corroborated by Bernard himself, that amyloid substance is found extensively throughout the animal economy, and is not confined exclusively to the liver, as was at first alleged. Neither is it necessary to allude farther to the theory that sugar produced in the liver is oxidised and converted, with the production of heat, into carbonic acid and water in the lungs, and that there is a reciprocity of function between these two organs in the generation and destruction of sugar, &c. These views, which were ushered into notoriety under the supporting authority of Liebig, do not now receive any consideration, and may, we think, be altogether forgotten.

Referring to the circumstance that under the existence of disease there is no amyloid substance discoverable in the liver, Dr Pavy proceeds to prove that this substance is susceptible of undergoing other transformations in the liver than into sugar. Having sufficiently shown that the *natural* destination of the amyloid substance in the liver is not the production of sugar, he indicates the grounds on which he holds that *fat* is the principle

towards the formation of which the amyloid substance *naturally* proceeds.* Under certain *unnatural* circumstances, however, amyloid substance is transformed into sugar during life, and this principle, finding its way into the circulation, makes its appearance in the urine. The discussion of this condition introduces the subject of the pathology of diabetes.

Until a comparatively recent period, diabetes has been placed in many systematic works on medicine, under the heading of Diseases of the Kidneys. And yet the malady was ascribed by Mead to a morbid state of the liver and bile; Prout was induced by long attention to be satisfied that the functions of the liver were deeply implicated in diabetes. Admittedly obscure in its pathology, the prevalent teaching has long associated the disease with the integrity of the digestive functions, and this view has been strongly corroborated by the remarkable and original observations of the late Dr Robert Macgregor of this city. Dr Macgregor demonstrated by physiological experiment and by chemical analysis, the presence of sugar in the juices of the stomach and in the excretions of the bowels of diabetic patients, and he inferred that a perverted action of the digestive organs was at the root of the malady. As it is now, however, quite established that a saccharine condition of the blood, and also of the urine, is always present in a small degree, even in the condition of perfect health, it is easily understood how the stomach juices should contain sugar without being in an unhealthy state, and equally easy to recognise how the unnatural increase of saccharine matter in the blood of a diabetic patient should give rise to a great increase in the saccharine condition of the ordinary secretions. The inferences derived by Dr Macgregor from his experiments are, therefore, no longer tenable, and we are brought back to the position we were in before his experiments were conducted.

According to Bernard's glycogenic theory the process of sugar production in the liver is balanced in a state of health by the process of sugar destruction in the lungs, and when the production of sugar is in excess of the destruction, the condition termed diabetes is the result. The sugar combustion theory, although at first advocated by Liebig,—we do not know his later views—does not, however, now find any supporters, and there is, indeed,

* Mr Banting, in a recently published edition of his pamphlet "On Corpulence," supplies some curious data on this point. He has observed that the use of sugar to the extent of 5 oz. during the week is, in his own case, speedily followed by an increase of 1 lb. in weight within that period, and throughout, his experience goes strongly to prove, that where there exists a disposition to take on fat, there is no article of diet that so effectually contributes to that result as sugar.

no evidence to show that sugar is susceptible of direct oxidation in the system, or that, as sugar, it is capable of contributing towards heat formation.

Without reference to Bernard's theories, the tendency of the most recent observations is to confirm and illustrate the earlier views of Mead, Prout, &c., and to show that diabetes has its origin in a faulty action of the liver. On all sides there is the evidence of abundant observation to prove that a saccharine sweetness of the urine, or glycosuria, can with certainty be produced artificially by injuries of the liver and of the nervous centres—what analogy there may be in that condition of nervous supply and of physical structure of the liver resulting from injury, and that condition which exists in the state of disease called diabetes, is a point requiring to be resolved by future observers. Meanwhile, it must be borne in mind that the mere presence of sugar in notable quantity in the urine does not constitute diabetes. Sugar, it is now proved, exists *normally* in the urine—it is *temporarily increased* by various known conditions affecting the liver and nervous centres—but it is *permanently* present in that state of disease which we recognise as diabetes. What, then, is diabetes? This, the pathological aspect of the subject, is investigated by our author with the same ingenuity and original powers of research that he exemplifies in following up the physiological views of the subject. We shall not, however, extend our notes of this section of the work, but can assure our readers that it fully confirms the favourable opinion we have formed of the manner in which our author has shed new light on the entire subject of diabetes.

We have reserved to the last the little we have to say in the way of adverse criticism, and we are glad to premise that it chiefly affects the author's exposition of chemical details. Throughout the chemical section there is an occasional want of completeness, very puzzling to the casual reader, and apt to lead to a depreciatory, although—as we are well satisfied—an unjust estimate of Dr Pavy's chemical knowledge. Thus at p. 12, while treating of Trommer's test, we are told that "where no sugar is present, the precipitated oxide of copper is not re-dissolved by the alkali added in excess." Against this absolute and unqualified statement we had pencilled on the margin a note—"unless ammonia is present," and we mentally resolved to rap our author's knuckles; but at p. 16 he shows he is aware of the fact referred to, for he says, "Under certain conditions there may be no fall of the sub-oxide, notwithstanding that sugar may be indisputably present," and he goes on to explain that ammonia and its salts have a solvent power over the sub-oxide of copper. A misleading

effect may be produced by these far-asunder counter-statements made regarding a fact that is simply expressed by saying that *the copper test cannot be applied to stale urine.*

At times, however, the author's chemistry is a little at fault. Thus at p. 13, while explaining the copper test for sugar, and after stating that "with the aid of *organic* matter a liquid is procurable in which free oxide of copper is held in solution. The *organic matter* selected for use must necessarily not have the power of effecting a reduction of the oxide, &c.," he proceeds to state that tartaric acid is of the kind required, and therefore, constitutes the agent ordinarily employed. Now, in referring the effect to the organic matter of the tartaric acid, our author is in error, for that effect depends, not on the organic matter, but on the double tartrate of potash and copper which is formed, and which *is soluble.* Another instance may be cited. When treating of Barreswil's liquid, a form of sugar test much used on the continent, and which is made with sulphate of copper, bitartrate of potash (cream of tartar), carbonate of soda, potash, and water, Dr Pavy states that "the carbonate of soda is introduced to neutralize the excess of acid in the bitartrate of potash," whereas, continues our author, "by taking at once the neutral tartrate [of potash] instead of the bitartrate, the call for the use of the carbonate of soda is dispensed with, and it appears to me better, on account of its being more simple, to prepare the test in this way." Here there is quite a misconception on the part of Dr Pavy. The carbonate of soda in Barreswil's liquid is not employed to neutralize the excess of acid in the bitartrate. That is done quite effectually by the potash which is added, as our author ought to have recollected, for it is thus that the neutral tartrate of *potash* is formed. The neutral tartrate of *potash and soda*, which is made by the addition of the carbonate of soda, is, however, a more readily and completely *soluble* salt, and hence is superior as a testing agent. Fehling's test is "modified" by our author by striking out caustic soda and substituting caustic potash, and this is the test he has for many years been in the habit of employing. The *modification* may have practically served our author's purpose, and it may be "more simple," but much might be said to show that it cannot be "better." However this may be, we trust he will in future recognise, and give a different explanation of the reasons that induce Barreswil and Fehling to employ soda in their testing liquids.

The entire ten woodcuts with which the book is illustrated, are bestowed on the chemical section. It is scarcely probable that any medical man, qualified to study and to be benefited by

the work, can, by any possibility, require his ideas to be refreshed with drawings of a urinometer, a common weighing balance, a graduated glass measure, a pipette, &c. Such illustrations might well have been omitted, and we trust that the trading chemical firm which has lent the woodcuts that adorn their popular catalogue, so familiar to the public, and to every first year's student, will not find an advertising medium in any republication of our author's book.

With regard to the bookmaking qualities of the work, we think it would be well in future editions, if the author would summarise his conclusions in a compact form, instead of giving them in the frequent iterations, which, diluted, disjointed, and diffused, require often to be sought for, among the arguments, illustrations, and details of the views of other observers. Some faults of manner might also be easily avoided, for, although expressions which frequently occur, such as "coming down as it were," and "alighting upon" the liver, blood, or heart of an animal, are sufficiently expressive, and personally characteristic of the author's vein of thought, they are unpleasantly peculiar, and sound somewhat "slangy" in a scientific work.

In conclusion, we are thankful for this book. The author throughout abstains carefully from theorising, and he makes very few statements that are not fairly supported by the facts he is capable of demonstrating. By eliminating much that overhung and mystified a subject already very obscure, he has given a much greater degree of precision to what is actually known, and he has brought into prominence several important considerations which have hitherto been overlooked. Although the book is not of that class which finds favour with the routine and busy practitioner, it will surely commend itself to the thoughtful physician and to the public teacher. We believe that the extensive diffusion of the views which it contains, will not only tend to give a higher tone to the general doctrines of physiology, but will, from their suggestive character, aid powerfully the advancement of practical medicine.